

## Conferences and Reviews

# Depression Followed by Dementia and Disordered Movement Clinicopathologic Correlation

*Discussants*

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### Clinical History

**J**OHAN C. ADAIR, MD\*: A 62-year-old man was brought to the hospital by his wife in April 1989 for evaluation of a progressive decline of cognitive function. His spouse first noted problems three years previously: as she underwent and recovered from a complicated surgical procedure, her husband displayed uncharacteristic indifference toward her condition. He then became withdrawn and "lost his sense of humor." Job performance also deteriorated, leading to retirement within a year.

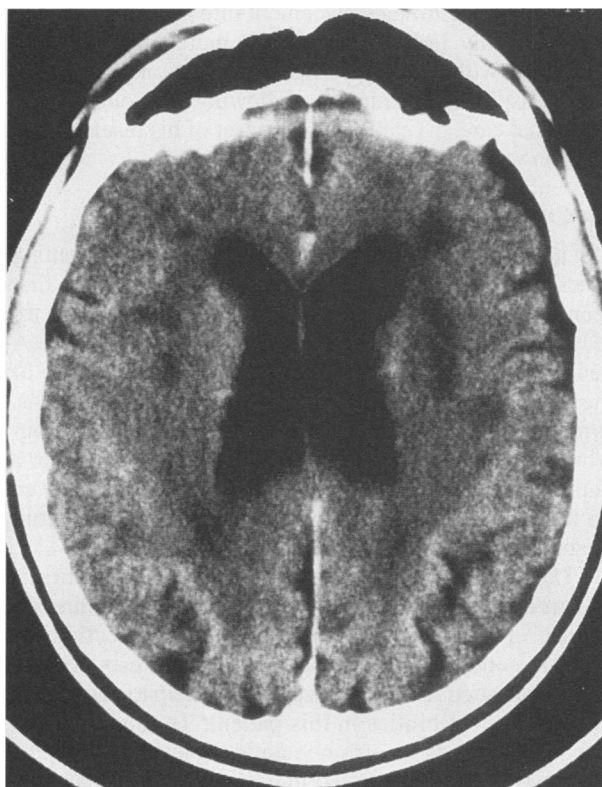
Evaluation in 1987 included psychometric tests that demonstrated impairment of auditory memory and geriatric depression scale scores indicating a moderately severe affective disorder. A cranial computed tomographic (CT) scan showed lucency of periventricular regions with mild cortical atrophy. Numerous blood tests showed normal values, including serum vitamin B<sub>12</sub> and folic acid levels, thyroid studies, rapid plasma reagin, serum copper and ceruloplasmin levels, and an erythrocyte sedimentation rate. Clinicians judged that the primary process was major affective disorder and treated him with tricyclic antidepressants.

Despite therapy, the patient's cognitive abilities declined. In addition to worsening memory, tremulousness of his hands developed. He also suffered anxiety attacks and had disturbing sensations that compelled him to disrobe.

The patient's history was remarkable for mild hypertension, although he had not required treatment for five years. No other family members had either dementia or a movement disorder. He was a mining engineer, but his occupation had never brought him into contact with manganese or heavy metals.

The results of a general physical examination on hospital admission were unremarkable. Speech was hypophonic with occasional paraphasic errors. The Folstein

Mini-Mental Status score was 18 of a possible 30; orientation was incomplete, recall was severely impaired, and he was incapable of writing sentences, copying figures, and performing serial subtraction tasks. Motor function showed diffuse atrophy without fasciculations and mild symmetric weakness in all extremities. A low-amplitude tremor was superimposed on upper extremity movements, but no dysmetria was observed. Gait was normal



**Figure 1.**—An axial computed tomographic scan through the lateral ventricles shows mild cortical atrophy with *ex vacuo* ventricular dilatation and diffuse periventricular white matter disease.

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aside from a decreased right arm swing. Deep tendon reflexes were symmetric at 3+ in the upper extremities, 2+ at the knees, and 1+ at the ankles. Plantar responses were flexor. Abnormal reflexes included a palmomental sign, snout and grasp reflexes bilaterally, and an increased jaw jerk.

A cranial CT scan again showed diffuse atrophy and patchy periventricular hypodensity (Figure 1), interpreted by a radiologist as consistent with Binswanger's disease. An electroencephalogram displayed symmetric slowing of background rhythm without focal features. Spinal fluid examination revealed no erythrocytes,  $1 \times 10^9$  leukocytes per liter (1 leukocyte per  $\text{mm}^3$ ), a normal glucose level, and a protein content of 0.65 grams per liter (65 mg per dl). A working diagnosis of vascular dementia was established, and aspirin was added to the medication regimen.

Increasingly agitated behavior resulted in a therapeutic trial of low-dose haloperidol in the spring of 1990. Shortly thereafter, the patient was observed in clinic to have a shuffling gait and increased appendicular tone. Parkinsonian symptoms persisted despite discontinuation of the neuroleptic drug. Over the next three months, incontinence developed, and he became markedly less ambulatory. At the time of placement into an extended-care facility in July 1990, he was nearly mute and practically immobile, with extremities fixed in a flexion posture. He died of aspiration pneumonia following 11 months of institutional care, 5 years after the onset of his disease. Permission was obtained for an autopsy.

## Discussion

**CHERYL P. HARRIS, MD\*:** This man died with a dementing illness that spanned at least five years. When he was first seen, he had signs and symptoms thought to reflect an affective disorder, but cognitive loss soon supervened. A neurologic examination several years into the course of the disease revealed diminished higher cortical functions, symmetric motor weakness, a diffuse tremor, and cogwheel rigidity. The extrapyramidal signs persisted after a neuroleptic medication was stopped. A CT scan showed no focal processes, and spinal fluid evaluation was non-diagnostic.

The differential diagnosis of dementia in this patient's age group is expansive. In the evaluation of dementing illnesses, emphasis is rightfully placed on detecting reversible conditions. The results of several tests done to investigate such reversible diseases can help to narrow the diagnostic possibilities in this patient. Thyroid function was normal, as was a serum vitamin B<sub>12</sub> level, making the diagnosis of dementia from either hypothyroidism or pernicious anemia untenable. The patient also had no history of substantial alcohol consumption, eliminating a possible alcohol-related disorder. Depression in older patients frequently is confused with dementia, and the results of psychological testing in this patient were suggestive of depression. Treatment with antidepressants, however, did

not alleviate the symptoms, and the course of the illness and progressively severe cognitive decline are not consistent with depression. Clinically serious depression, though, may frequently coexist with many of the primary dementias.<sup>1</sup>

Another consideration in evaluating dementing diseases is the time course of various symptoms accompanying the illness. Paraneoplastic disorders, such as limbic encephalitis, may give rise to personality changes and memory disturbances<sup>2</sup> and should be considered in middle-aged patients. Lung cancer, particularly oat cell carcinoma, is the most common tumor underlying this condition. Although encephalopathy may be the presenting feature in this situation, an occult malignant neoplasm would have progressed to a symptomatic state over the five-year course of the patient's illness. Similarly, the diagnosis of Huntington's disease can be eliminated. Although personality alterations and failing intellect may precede the onset of the movement disorder by several years,<sup>3</sup> the classic choreiform movements eventually supervene.

The time course of the dementing illness itself may also serve to differentiate it from the others. The mean duration of disease in 45 patients with Creutzfeldt-Jakob disease was 11.5 months, with some of the patients surviving only 3 months after the start of their illness.<sup>4</sup> Other factors that do not favor the diagnosis of Creutzfeldt-Jakob disease in this patient include the lack of startle myoclonus, which is frequently described in patients with this disease, and an electroencephalogram that showed symmetric slowing but not the classic pattern of "burst suppression" commonly seen in this disorder.<sup>4</sup>

The dementia complex associated with the acquired immunodeficiency syndrome is defined by disabling cognitive impairment usually accompanied by motor dysfunction, behavioral change, or both.<sup>5</sup> There are a number of reasons why this diagnosis is not appropriate in the patient under discussion. No risk factors for human immunodeficiency virus infection are mentioned in the clinical record. The serologic test for human immunodeficiency virus antibodies is not mentioned, perhaps because it was not done. As alluded to previously, a five-year illness duration without other systemic signs of the acquired immunodeficiency syndrome would be distinctly unusual.

Another category of diseases to consider in this patient includes the vascular dementias. Some authors think that multiple cerebral infarcts are the second most common cause of dementia after Alzheimer's disease.<sup>6</sup> The clinical history generally described with multiple infarct dementia is an abrupt occurrence of focal neurologic symptoms and a stepwise deterioration of neurologic function.<sup>7</sup> In addition, the strokes should be visible on neuroimaging studies. None of these characteristics are described in this patient.

Serious consideration needs to be given to the diagnosis of Binswanger's disease (subacute arteriosclerotic encephalopathy). In 1894, Binswanger described cases of "slow progression of mental deterioration" and white

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matter disease in patients with chronic hypertension.<sup>6</sup> These patients have a spectrum of symptoms, and some may even be asymptomatic.<sup>8</sup> The most commonly described symptoms include gait apraxias, motor dysfunction, urinary incontinence, and pseudobulbar palsies.<sup>9</sup> Although the patient presented here is described as having diffuse symmetric weakness, pseudobulbar signs are not mentioned, and incontinence developed late in the course of his disease. In addition, although he apparently did have high blood pressure in the past, the hypertension was thought to be quiescent and required no medical treatment for some time before he was seen. A CT scan of the brain in our patient showed periventricular lucencies, and the radiographic picture suggested Binswanger's disease to the radiologist. Hachinski and co-workers coined the term "leukoaraiosis" to describe this periventricular leukomalacia,<sup>10</sup> a term that may or may not be synonymous with Binswanger's disease. Although the imaging study is consistent with this diagnosis, the clinical findings and the absence of chronic uncontrolled or poorly controlled hypertension argue against a diagnosis of Binswanger's disease.

Another less common cause of dementia in elderly persons is progressive supranuclear palsy. The cardinal feature of this dementia, in addition to a progressive dementia and extrapyramidal signs, is a supranuclear ophthalmoplegia primarily limiting vertical gaze.<sup>11</sup> Although the patient did have a tremor (which may occur in progressive supranuclear palsy), the eye movements were described as being normal and apparently remained so throughout the course of the patient's illness. This is not compatible with the diagnosis of progressive supranuclear palsy.

The most common primary dementia in the United States is Alzheimer's disease. The cause of this disease is unknown, but evidence of a genetic predisposition is mounting.<sup>3</sup> The definitive diagnosis of Alzheimer's disease requires a neuropathologic examination,<sup>12</sup> but several neurologic signs and symptoms point towards this diagnosis. In addition to cognitive decline, speech disturbances are common initial findings.<sup>13</sup> These include repeating words or phrases (echolalia), dysnomia (especially for proper nouns), and problems in understanding written or oral speech. Various motor apraxias may be seen early in the course of the disease, and frequently visuospatial dysfunction is present. Extrapyramidal signs such as tremor and increased motor tone are uncommon early in the disease course but may appear as the illness progresses.<sup>3</sup> As there are no clinical or biochemical criteria that are diagnostic of Alzheimer's disease before death, the condition cannot be definitely excluded in the patient under discussion. History obtained from the patient's wife, however, does not seem to indicate a prominent speech disorder or a loss of motor skills early in the illness course, but rather a diffuse personality change and memory loss. The duration of Alzheimer's disease is usually between four and ten years,<sup>13</sup> and the five-year period of illness of our patient falls into this range.

Another uncommon form of primary dementia is

Pick's disease (lobar sclerosis). Although the clinical findings in this condition are not specific, the disease can be differentiated pathologically from other dementing illnesses. Clinical features frequently described with Pick's disease include signs of temporal lobe or limbic system origin, including lapses in social conduct, disinhibition, bulimia, and gluttony.<sup>14</sup> In addition, radiologic imaging studies show, as the name of the condition implies, lobar atrophy more prominent in either or both the frontal or temporal poles than that which is seen in Alzheimer's disease.<sup>15</sup> Although it cannot entirely be discarded as a possible diagnosis, none of these features were prominent in the patient under discussion, and Pick's disease is unlikely.

A final class of dementing illnesses to consider includes two conditions that are perhaps linked more by their histologic findings than their clinical aspects: Parkinson's disease and diffuse Lewy body disease. The clinical features of idiopathic Parkinson's disease are familiar to physicians—bradykinesia with rigidity, resting tremor, and a loss of the postural reflex.<sup>16</sup> The cognitive capacity of patients with Parkinson's disease remains a controversial issue. Reports range from the initial one by James Parkinson, who was of the opinion that intellectual function was unaffected in these patients,<sup>16</sup> to an estimate that substantial dementia occurs in 20% to 40% of patients.<sup>17</sup> Patients with this disorder initially show a movement disorder, and dementia appears in the later stages of the disease, if at all. Although this patient had a low-amplitude tremor and an increase in tone on examination, his decline in cognitive function clearly predated and surpassed any extrapyramidal signs.

Lewy bodies, the pathologic hallmark of Parkinson's disease, were first described in 1912 by Lewy<sup>18</sup> and were found primarily in pigmented neurons of the brain stem. In 1961, however, Okazaki and associates described the presence of Lewy bodies in the medium-sized neurons of the cerebral cortices in patients with dementia.<sup>19</sup> In time, diffuse Lewy body disease, as this condition is now called, has become recognized as a separate clinicopathologic disorder from Parkinson's disease. Diffuse Lewy body disease is thought to occur more frequently in men than in women,<sup>18</sup> and the mean age of onset in a report of 15 patients was 72 years.<sup>20</sup> In a review of autopsy results of 216 demented persons, diffuse Lewy body disease was the second most prevalent disorder, outranked only by Alzheimer's disease.<sup>21</sup> Unlike some of the other primary dementias, no distinct genetic patterns have been found to suggest a familial tendency to the condition.<sup>22</sup> Although the disease is still not commonly diagnosed before death, some authors think that it encompasses clinical features unique enough to differentiate it from other primary causes of dementia. These features include psychiatric symptoms, impaired gait, abnormalities in tone, and resting tremor and were prominent early symptoms in some patients.<sup>21</sup> Extrapyramidal signs are usually overshadowed by dementia, however,<sup>18</sup> in contrast to Parkinson's disease. To further cloud the clinical differentiation of dementias, there have been reports of patients with suffi-

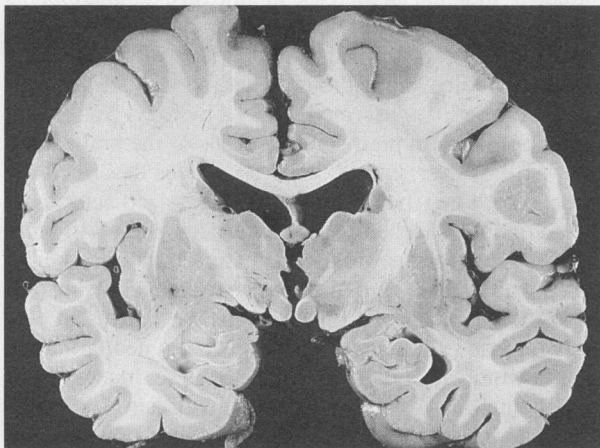
cient pathologic criteria for both diffuse Lewy body disease and Alzheimer's disease.<sup>22</sup>

The course of the illness of this patient is most consistent with the clinical history of diffuse Lewy body disease, with prominent dementia but underlying cogwheel rigidity, tremor, and a shuffling gait. Evaluation of this man's extrapyramidal symptoms is complicated by his being given haloperidol, which is well known to induce parkinsonian symptoms. The presence of tremor before the medication's administration and the persistence of tremor and cogwheel rigidity after the drug's withdrawal would seem to indicate a primary bradykinesia rather than secondary extrapyramidal effects. Although other dementing illnesses cannot be excluded with certainty, diffuse Lewy body disease is the most likely diagnosis.

### Neuropathologic Examination

JEANNETTE J. TOWNSEND, MD\*: The general autopsy revealed that an aspiration pneumonia was the cause of death.

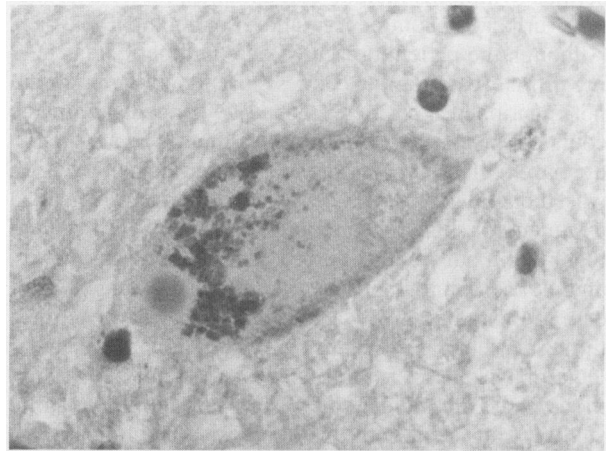
On neuropathologic examination, the brain weighed 1,375 grams and showed minimal frontal atrophy. Mild dilatation of the lateral ventricles was evident on coronal sections with no identifiable focal lesions (Figure 2). Pallor of the substantia nigra was the only grossly visible abnormality on axial sections of the brain stem. The cerebellar hemispheres were normal. Mild atherosclerosis of the right posterior cerebral and left middle cerebral arteries was found.



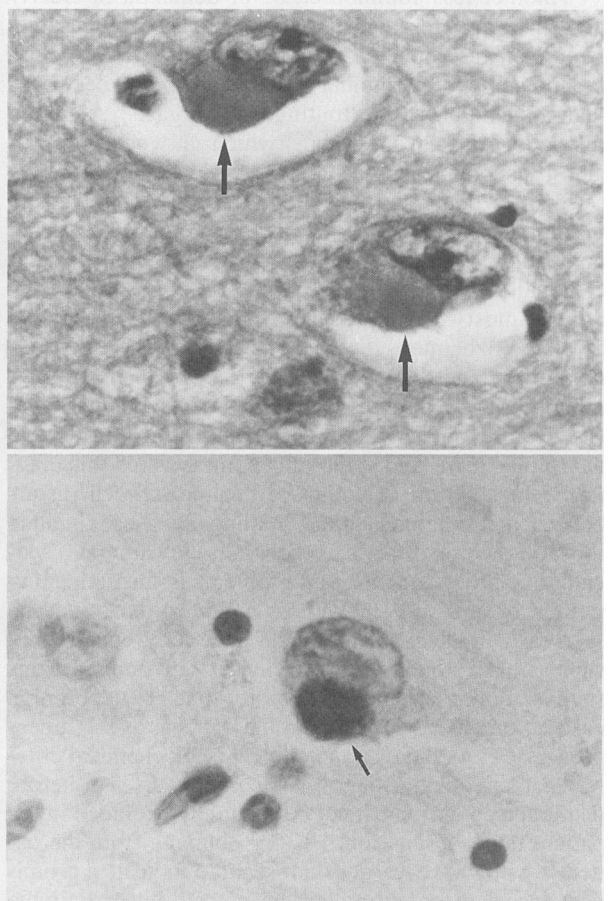
**Figure 2.**—A coronal section of the brain shows minimal atrophy with mild *ex vacuo* dilatation of the lateral ventricles.

Histologic sections of the substantia nigra revealed a loss of pigmented neurons with incontinence of melanin pigment. Numerous intracytoplasmic, rounded, pink inclusions (Lewy bodies) were found in the remaining neurons (Figure 3). Similar Lewy bodies, although less distinct, were present throughout the frontal and parietal cortices (Figure 4, top). These Lewy bodies reacted positively with monoclonal antibodies to ubiquitin (Figure 4, bottom). Neither senile plaques nor neurofibrillary tan-

gles were identified in the hippocampus or cortex. No vascular or white matter changes were found to suggest Binswanger's disease.



**Figure 3.**—A round eosinophilic Lewy body with a surrounding halo is seen in a pigmented neuron of the substantia nigra (hematoxylin and eosin stain, original magnification  $\times 800$ ).



**Figure 4.**—**Top,** Two small cortical neurons are depicted with cytoplasmic ill-defined Lewy bodies (**arrows**) (hematoxylin and eosin stain, original magnification  $\times 800$ ). **Bottom,** Immunohistochemical staining with the antibody to ubiquitin shows a positive reaction in an intracytoplasmic Lewy body (**arrow**) (peroxidase stain, original magnification  $\times 800$ ).

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These findings are typical of diffuse Lewy body disease. At autopsy, these patients usually show only minimal atrophy of the cerebral hemispheres with pallor of the substantia nigra and locus ceruleus. On histologic examination, patients with diffuse Lewy body disease show neuronal loss and pigmentary incontinence in the substantia nigra with intracytoplasmic Lewy bodies.<sup>18</sup> Lewy bodies are also found in many other areas of the brain stem and basal ganglia, including the locus ceruleus, dorsal motor nucleus of the vagus nerve, and the substantia innominata. Within the small or medium-sized neurons of the deeper cortical layers, similar intracytoplasmic inclusions are found. They are not as distinct as those in the pigmented neurons but tend to be ill-defined and paler without a surrounding clear halo.<sup>18</sup> Almost any area of the cortex may contain Lewy bodies, but the parahippocampal, anterior temporal, and cingulate gyri are more frequently affected. The average number of cortical Lewy bodies ranged from 10 to 12 per section of cortex examined by one group of researchers.<sup>23</sup> Immunohistochemical staining with antiubiquitin, which is a polypeptide involved in an adenosine triphosphate-dependent breakdown of abnormal cellular proteins,<sup>22</sup> is strikingly positive and usually demonstrates many Lewy bodies that are not seen with hematoxylin and eosin stains. By electron microscopy, Lewy bodies are composed of filamentous and granular material with a halo formed of filaments around a dense core. The cortical Lewy bodies are similar but lack the filamentous halo.<sup>18</sup>

Many patients with diffuse Lewy body disease are misdiagnosed clinically with Alzheimer's disease because of the pronounced dementia that occurs during the course of the disease. The bradykinesia and other symptoms of parkinsonism that these patients may exhibit should alert clinicians to the possibility of diffuse Lewy body disease. In some instances, pathologic changes of both Alzheimer's disease and diffuse Lewy body disease are found in the same patient: these patients have been described as having the "Lewy body variant" of Alzheimer's disease.<sup>22</sup>

An increasing number of cases have been recognized over the past 30 years since the first case of diffuse Lewy body disease was reported.<sup>19</sup> As the cortical Lewy bodies may be difficult to see, they can easily be missed on a standard hematoxylin-eosin stain. Immunohistochemistry

for ubiquitin is warranted in any case in which there is a clinical diagnosis of dementia and Lewy bodies are found at autopsy within the substantia nigra.

#### Acknowledgment

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